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2RT: EARLIER INTERVENTION FOR AMD

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2RT: EARLIER INTERVENTION FOR AMD

As multimodal imaging redefines diagnosis, a new laser technology may make early interventional treatment possible for some types of AMD.

As the ability to detect and diagnose age-related macular degeneration (AMD) has evolved to encompass earlier stages of the disease, the effort to develop earlier treatments has intensified. Recent research efforts have yielded some interesting results. Retina Today *hosted a roundtable discussion during AAO Chicago 2018, chaired by Ellex Chief Medical Officer, David Lubeck, MD. The roundtable brought together a group of leading international experts in AMD to discuss changing treatments for the disease and how they envision the future (Figure 1).*

Figure 1. Leading experts gather during AAO 2018 in Chicago. Left to right: David Lubeck, MD (moderator); Robyn Guymer, AM, MBBS, PhD; Frank Holz, MD; David Chow, MD; Rishi P. Singh, MD; and Netan Choudhry, MD, FRCS(C).

THE UNMET NEED FOR EARLY AMD TREATMENT

▶ We have seen a recent focus on the social and human costs of advanced AMD (Figure 2),[1,2] which highlights the need for interventions to diagnose and treat the condition earlier in the disease process. How has this new focus changed the way you treat AMD?

Frank Holz, MD: It is a huge unmet need. As we have come to understand the enormous burden that patients shoulder in the late stages of this disease, it has become obvious that an intervention that prevents the late-stage disease from developing is needed. Today, we can treat the neovascular phenotype quite successfully, but we do not have any efficacious treatment for late-stage dry AMD with geographic atrophy (GA). An early intervention to slow progression of the disease would help enormously.

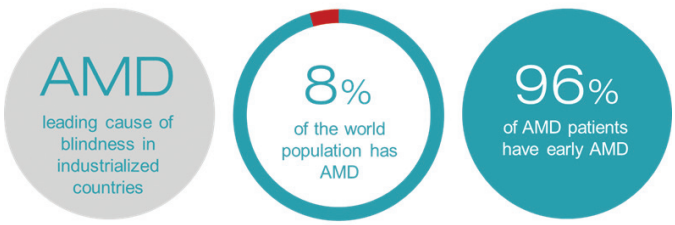


Figure 2. AMD has a significant effect on the global population.[1,2]

> Patients and physicians are desperate...I am pleased that we now can offer a treatment to patients with early AMD that may slow down progress of the disease, thereby lowering their risk of losing vision.
>
> —David Chow, MD

David Chow, MD: One of the things we know about patients who do well on AMD therapies is how important their baseline VA is. If we can preserve their vision at a much earlier stage, when their vision is quite good, then their long-term outcome can be quite good as well. The benefit of early intervention is a consistent factor we have been able to extract from all the studies we have ever done on anti-VEGF therapy.

Robyn Guymer, AM, MBBS, PhD: The treatments for wet AMD are quite efficacious, but they are also quite expensive and are a huge burden in terms of patients' quality of life. Patients would fare much better if we could intervene early, so we would not reach a point where we need to rely on anti-VEGF treatments.

Dr. Chow: Prof. Holz hit it on the head. Patients and physicians are desperate for something to treat patients with dry AMD and resulting visual loss. We know many patients who suffer significant visual loss from this disease are patients with dry AMD who go on to develop GA. So many patients in our practices are suffering. They are always walking in my door saying, "Why is it that you can give the other patient a needle, but you cannot do anything for me?" I am pleased that we now can offer a treatment to patients with early AMD that may slow down progression of the disease, thereby lowering their risk of losing vision.

DIAGNOSING AND STAGING AMD

▶ As we discuss wet and dry AMD, and early, intermediate, and late-stage disease, we should ensure we are clear about these terms. Please describe the different stages of AMD. How do new diagnostic technologies allow you to detect these stages, and how does this impact your choice of treatment?

Prof. Guymer: It makes matters confusing that many physicians use the term "dry AMD" when referring to late-stage GA or any disease that is not "wet" AMD. It is critical that we all use the same terminology, particularly when we are developing treatments that depend on the disease stage. Practitioners have tended to lump all AMD that is not wet into the dry category. Perhaps this was acceptable when there were no specific treatments for AMD at different stages of progression, but as we now start to discuss intervening early, we need patients and other doctors to understand what stage they have.

Prof. Holz and I were part of the Ryan Beckman Initiative, so we would like people to use the Beckman Classification's five subgroups (Table 1).[3]

Early AMD is defined based on the size of drusen, which is medium. Intermediate AMD involves either large drusen or medium drusen plus pigment. Finally, in late AMD, there may be atrophy or neovascular disease.

With multimodal imaging, we are now able to detect atrophy earlier and earlier, which is why the Classification of Atrophy Meeting focuses in part on trying to standardize how we define the changes we see on OCT. Prof. Holz and I both contributed to a paper earlier this year that classifies complete atrophy and incomplete atrophy based on which layers of the OCT are missing.[4] Complete atrophy includes photoreceptor and retinal pigment epithelium (RPE) loss, and incomplete atrophy has a lesser degree of RPE damage and outer retinal atrophy. We are trying to get everyone to use these terms so that we can all contribute to trials that determine the risks associated with these stages.

▶ Diagnostically, how would you approach a patient with early or intermediate AMD?

Netan Choudhry, MD, FRCS(C): Traditionally, prior to the LEAD trial,[5] our options for counseling patients about the available therapies were limited, and these patients were somewhat neglected. We know that the AREDS vitamins are helpful for a certain subclass of patients with AMD, but now we are evaluating patients in the context of a new treatment modality, namely 2RT. We look at multimodal imaging, OCT, the clinical picture, the size of the drusen, and the presence or absence of GA. Even nascent GA will be important as we evaluate these patients, as Prof. Guymer described.

Rishi P. Singh, MD: It might be worth pointing out that all of these stages have two really important features that clinicians use frequently. First, they help us to determine the level

TABLE 1. AMD: BECKMAN CLASSIFICATION[3]

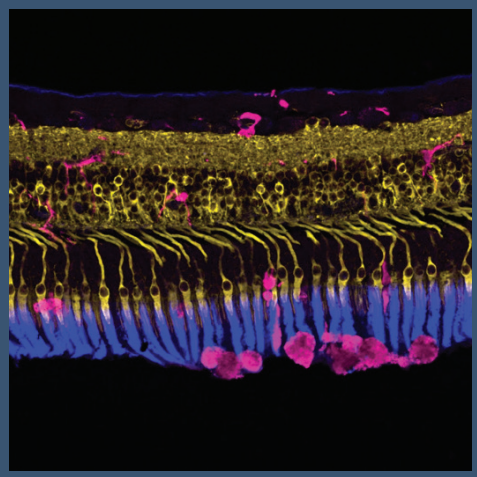
1. No AMD (normal aging changes)
2. Early AMD
3. Intermediate AMD
4. Late AMD, neovascular (wet AMD)
5. Late AMD, GA (dry AMD)

of visual detriment, so we can say, for example, that a patient has intermediate AMD and visual decline as a result. Second, the stages allow us to determine the disease progression, and we know that patients with late-stage AMD will progress at a different rate than those who have earlier disease. That allows us to give our patients a prognosis.

LEAD TRIAL OF 2RT RETINAL REJUVENATION

2RT is a nanosecond pulsed laser (Table 2). The technology was developed by Ellex with the goal of eliminating thermal damage to the neural retina, thus sparing the photoreceptors from apoptosis during retinal laser treatment. It induces a mononuclear cell response, including the release of microglia (Figure 3). The 2RT laser's mode of action is the combination of nanosecond pulses and engineered Nanopix Technology (Ellex), which produces a proprietary pixelated beam to a very specific proportion of RPE cells, subjecting only targeted individual cells to undergo apoptosis and allowing for a natural healing response to restore retinal function. This ensures targeted treatment of individual RPE cells. No other retinal laser delivers such a short pulse, nor produces a pixelated beam.

TABLE 2. THE KEY PARAMETERS OF 2RT
3 nanosecond pulse duration
400 µm spot size
Nanopix Technology
Pixelated beam profile



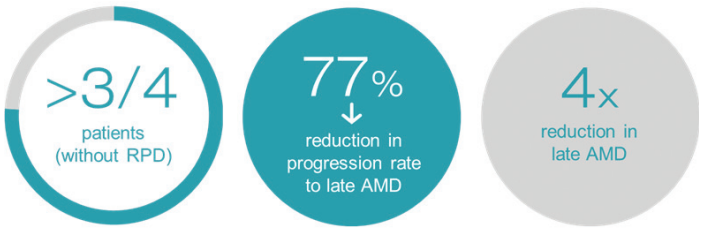
Courtesy of Professor Erica L. Fletcher MSc Optom, PhD (Department of Anatomy and Neuroscience, the University of Melbourne, Australia).

Figure 3. 2RT induces a mononuclear cell response, including the release of microglia (pink). In this image, the retinal microglia are shown extending their processes through the outer nuclear layer towards the laser treatment site.

▶ In 2018, the LEAD randomized clinical trial of 2RT technology showed that it may slow progression to late AMD in patients without reticular pseudodrusen (RPD) (Figure 4).[5] What do you consider the role of 2RT in your clinical practice?

Prof. Guymer: It was important to do a properly conducted randomized clinical trial, which has been lacking for subthreshold lasers in general. This was the first robust clinical trial for 2RT, and results showed that, overall, there was no benefit of the laser treatment in slowing progression to late AMD. However, in a post hoc analysis, there appeared to be a differential treatment effect depending upon the presence of RPD, with those without RPD having less progression and those with RPD having a greater risk of progression to late AMD in the treatment group. It is very important to remember that we need to validate the results with a second trial. We must have a replication study showing the same results.

Prof. Holz: We would very much welcome an opportunity to slow progression. Since we learned about the encouraging results of the LEAD trial of the 2RT system led by Prof. Guymer,[5] we have been reflecting on the design of a study to validate the post hoc analyses. Imaging technologies now allow us to clearly detect RPD, which sit atop the RPE differently from sub-RPE drusen.



- 36-month, multicenter, randomized, sham-controlled trial.
- 292 patients enrolled had bilateral large drusen without signs of atrophy on OCT.
- Participants were randomized to 2RT or sham treatment at 6-month intervals.
- Multimodal imaging showed that overall, there was a positive trend towards slowing disease progression to late AMD, but this did not reach statistical significance.
- The benefit of 2RT was shown in a post hoc analysis, where progression to late AMD was significantly slowed for 222 participants without coexistent RPD.

Figure 4. The 2RT LEAD study results.[5]

Prof. Guymer: The results look very promising. Subthreshold nanosecond laser treatment may help slow progression in patients without RPD, and the basic science certainly is very solid. The LEAD results were derived from a post hoc analysis, and we uncovered an interesting finding once we drilled down to look at treatment effect modification analysis. In this post hoc analysis, patients were randomized on the basis of the

RPD. Until we do that and find the same results, we have a promising result, but not a proven intervention at this stage.

Dr. Chow: The work that Prof. Guymer has done is groundbreaking. It is essential that someone has actually done a proper prospective trial with subthreshold laser technology, because many other technologies with subthreshold lasers have suffered as a consequence of not having a properly run prospective trial.

In the post hoc analysis, Prof. Guymer's trial highlights a clinical finding about RPD that goes beyond the average retina specialist's diagnostic experience. Although we all know RPD, we have never used it as an important piece of diagnostic information that could strongly influence our treatment decisions. I think Prof. Guymer's work highlighting RPD is such an incredibly important factor in determining whether this technology may or may not be effective. In fact, I would love to understand how you defined RPD. Was that purely photos? Was it OCT? Was it scanning laser ophthalmoscopy?

Prof. Guymer: Right from the beginning of the design phase, we wanted to look for RPD as a variable. What we did not think about was whether the effect of 2RT would differ depending on the presence or absence of RPD. We followed a very strict definition of RPD that occupies about a page of the paper. Basically, we wanted patients to have at least five RPD spread over more than one OCT scan and validated on another *en face* OCT image. We needed to see RPD definitively on two *en face* images because an OCT scan shows the central cube, and RPD can occur outside the cube.

We classified RPD as definitely, possibly, or definitely not present, and analyzed the results, comparing definitely versus the rest. We determined that 2RT's greatest potential efficacy lay with patients without RPD.

Dr. Chow: You have written another paper that elegantly looked at the rate of RPD and its risk of causing GA, which was about 12% to 14%.[6] That was based on fundus photography.

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If you look at the literature on RPD, it goes from those numbers up to 92% in a few papers.[7] Based on your results, it seems as though the way we classify RPD for 2RT will become critically important.

Prof. Guymer: Correct. According to the work of Christine A. Curcio, PhD, from the United States,[8] we can find RPD in almost anyone. It will be interesting to learn in the future if patients can afford to have a small amount of RPD and still benefit from 2RT. Some subjects were predominately RPD, but they had to have at least one standard drusen to get into the trial. Going forward, we have to ask whether we should include patients with RPD in 2RT studies. I do not think we should automatically exclude them, because it would be a shame to deny any chance to slow down progression to patients who are at risk. Just as one trial requires verification before we can say treatment has value for one group, we also need to see verification in a second trial of whether it lacks value for another population.

▶ Dr. Singh, as a physician who has not used 2RT yet, how are you presently managing early AMD? How do you think you might incorporate 2RT into your practice?

Dr. Singh: Right now, it is about waiting and watching the patient. We do not have many options for our patients with this condition. We do give them AREDS vitamin therapy and the ForeseeHome monitoring device (Notal Vision), which has been shown to improve the ability to detect early conversion to exudative AMD at home, so we can get them in with earlier VA changes.[9] Beyond that, we do nothing more. If we had a good treatment option for these patients that was proven in a large trial, we would be more than willing to adopt it and probably use it for many of our patients.

INITIATING 2RT FOR INTERMEDIATE AMD

▶ Let us discuss the clinical scenario of patients with intermediate AMD. How would you describe these patients?

Prof. Holz: Although they can have perfect 20/20 vision, often they have functional deficits. For example, they take longer to adapt from the sunny outdoors to a dark room. Dim light is terrible for them. It would be a second aim of any treatment to not only halt progression to late stages of AMD, but also perhaps to improve vision in the intermediate stage of the disease. We have not yet learned whether AREDS vitamin supplements for intermediate AMD will produce any improvement. The hypothesis is that if a treatment can get rid of excessive extracellular material, perhaps photoreceptors and the RPE

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will function better, but this needs to be tested.

Dr. Choudhry: That is one of the things we see in our practice as well. Patients with intermediate AMD start to complain of visual issues that generally did not exist in the disease's early stages because the drusen burden or RPE changes were low. At the intermediate stage, they have decreased retinal sensitivity, slowing dark adaptation, and metamorphopsia from larger drusen that are starting to develop. We get patients involved in vision rehabilitation therapy or using magnifiers, and they experience benefits from that process very quickly. It is a critical stage within the AMD spectrum when intervention would really be ideal.

▶ Looking at the clinical and diagnostic spectrum, what are your treatment criteria to initiate 2RT?

Dr. Choudhry: Currently, we look to the LEAD trial for guidance in terms of which types of patients should be offered treatment with 2RT. As we have just discussed, RPD is one factor for exclusion. It is not indicated for patients with GA. When there is nascent GA hiding and about to become full-thrust, that would not be an ideal situation to offer 2RT. Ideally, we would like to offer it earlier in the disease progression, particularly to our patients with intermediate AMD.

Prof. Holz: In Europe we do not offer the treatment at this stage. Results from the LEAD trial are promising,[5] but the next steps of another clinical trial informed by the LEAD trial need to take place before it gets approval from the regulatory authorities. We look forward to the commencement of that trial.

Dr. Chow: One practical issue is that since we received the 2RT laser in our office, our referrals have not met the inclusion criteria: intermediate AMD with no visual loss. The more common patient has already started to suffer some overt visual loss and has early GA. That has been the issue for me. Prof. Guymer, I would love to hear your comments. I know that GA was excluded in the trial criteria, but do we know if, for example, early GA is an absolute "no" with this technology?

Prof. Guymer: We do not know because they were not in the trial. We have tried to look back at the data to see if there is any indication that a small patch of nascent GA could be reversed by causing the RPE to sort of bridge the gap. Looking closely at the trial's results, there may be a few instances where the nascent GA seemed to improve for whatever reason, so it could be possible to use 2RT when there are very small amounts of nascent GA. However, if you want an early-stage endpoint, then what are we going to measure if patients are starting with atrophy?

It will be interesting to see what the US FDA wants us to do. Will they want us to treat patients and observe all the way to GA, in which case we could potentially include some nascent atrophy and determine whether we can slow it down? As we continue to follow patients from the LEAD trial, we may find that we have slowed the progression from nascent to full-blown GA. It is possible that treatment may be of help to the rest of the eye.

The other interesting thing, of course, is the bilateral effect. In the animal studies, there seemed to be some benefit to the other eye,[10] and our very early pilot study showed this as well.[11] It may be possible to treat one eye and see some benefit to the other eye in slowing down progression. We have a lot to learn about this from the preclinical data because there are measurable indicators in both eyes that appear to suggest we are improving the removal of extracellular debris.

Prof. Holz: Perhaps to the point, we should create the same experience and offer the same options to patients who present with symptoms and show a precursor to atrophy on their B-scans. It would be a shame to exclude them from future treatment, particularly because atrophy is present in such a high proportion of patients. Is incipient atrophy the point of no return or not? We do not know. In any case, we should continue to develop treatments that show efficacy in the presence of GA in terms of slowing lesion enlargement.

Dr. Chow: I agree with you, but I was discouraged by the strong connection between RPD and GA in the post hoc analysis.

Prof. Guymer: It is the patients with RPD who are most affected by the dark adaptation problems. They potentially progress to atrophy more quickly. They are the very patients you really want to treat.

In fact, drusen by itself may be less of a risk than we have

previously understood. In the AREDS study, they were not able to look at RPD in everyone.[12] They did not have all the multimodal imaging we are using. As a result, we do not know the risk of progression for a patient who has drusen without RPD. The two things together are clearly not good news.

▶ There have been previous studies on laser treatment of AMD. How is the LEAD trial different?

Prof. Guymer: The first studies go back many decades. Don Gass actually noticed serendipitously that when he used a thermal laser on diabetic patients, their drusen resolved.[13] In the 1990s, researchers in both America and Europe tried using a thermal laser to reduce drusen, and some of them were stopped due to concerns about neovascularization as a complication. Subsequently, Cochrane's analysis showed that was not the case.[14]

Previous studies focused on the old thermal lasers. In contrast, the nonthermal 2RT laser, has a very different mechanism of action. We cannot extrapolate LEAD findings to other types of lasers, even subthreshold lasers. As far as I know, LEAD is the only randomized clinical trial of a subthreshold nanosecond laser for AMD.

TEACHING PEERS TO CLASSIFY AND REFER AMD

▶ We have discussed the use of advanced imaging to perform a more detailed analysis of AMD, and then tailoring therapy accordingly. What does this mean for primary care doctors referring patients to you?

Dr. Choudhry: One of the things that has come out of this trial, where a paradigm shift is upon us and we are about to embark on a possible new treatment for AMD, is the responsibility to educate peers more about the nonexudative form of AMD. Most primary eye care providers can identify a subretinal hemorrhage, pigment epithelial detachment, and so forth. But now they may need to recognize all the subtleties of the different types of drusen through a GA classification system. A great deal of new nomenclature is being developed to describe the anatomy of nonexudative AMD. All of this will inform the development of inclusion criteria for the next trial or actual treatment that we are rolling out, like 2RT.

Prof. Guymer: In Australia, optometrists see many of these patients and refer them to ophthalmologists or for studies. Many of our optometry practices have OCT, but they need to know what they are seeing, so now we are actively teaching optometrists what to look for on OCT.

It took us about 3 years to recruit for the LEAD trial, which is a long time given the prevalence of AMD. Optometrists

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referred patients with drusen plus pigment, and we found that about 40% of these people had nascent GA. The referring clinician would think they had early AMD, but when we looked more closely, they already had the beginnings of atrophy. Forming a patient cohort with drusen plus some pigment and no nascent GA took quite some time, but we could reduce that time by teaching optometrists to identify the necessary characteristics on OCT. Eventually, we hope that we can build a registry that enables us to recruit much more quickly.

Prof. Holz: As the classification develops, it will become more complex. We have simplified this classification over the past decades, and now high-resolution imaging modalities give us a new level of granularity. Yes, we need to address the role of optometrists as the first contact, but I am convinced that artificial intelligence and machine learning will permit the imaging modalities themselves to make assessments and classifications right away. For example, we will not have to search for RPD in each and every B-scan in the future. Artificial intelligence will help identify these patients.

Dr. Choudhry: As Prof. Guymer mentioned, the term "dry AMD" should be much more specific because the treatments are likely going to be aimed at subtypes within the spectrum of nonexudative AMD.

Prof. Guymer: Yes, it is very important because when patients come and tell us they have been told they have dry AMD, physicians say, "Well, it is too late." But when we take a closer look, they have actually got intermediate AMD that is not wet, so their doctor has called it dry. If we all use the same terms to describe each condition more clearly, at least the right patients will be referred for trials, and no one will be missed.

Prof. Holz: Even for late dry AMD with GA, there is huge variability. We now have predictive factors that explain some 40% of morphological factors in future progression rates. In order to

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>
> —Robyn Guymer, AM, MBBS, PhD

select the right patients that may be helped by a specific intervention in GA trials, we need more complex, detailed classification.

▶ Let us use this forum as an educational tool. Is there a tailored version of AMD diagnosis that optometrists and comprehensive ophthalmologists could use in their daily practices to help them master the disease's complexities?

Prof. Guymer: In Australia, we are trying to get optometry to classify AMD using the Beckman Classification as the first step.[3] Next, we look for RPD, which requires more advanced imaging and a color photo, as well as the ability to read the signs, for accurate diagnosis. Beckman plus RPD analysis go a long way.

Dr. Singh: Beckman is the first of the new classifications in the OCT era, and it has been important to learn as a lay clinician who is a part of many studies. One of the interesting things about this approach is it shows that the presence of drusen alone does not constitute AMD. That was probably the biggest of many takeaways from the LEAD trial for me. I tell my patients about this all the time when I receive referrals for suspected AMD. Hopefully our optometry colleagues are receiving this message as well.

ENRICHING PATIENT EDUCATION

▶ We have laid out some of the more detailed ways you diagnose and approach AMD. Will this affect your conversations with patients?

Dr. Singh: To just say the word "retina" is deceiving to the patient, who does not have that level of understanding. I start by explaining AMD in terms of the eye as a camera, using its architecture to discuss the structures of the eye and levels of AMD. I have many figures in my office to demonstrate what AMD looks like in various disease states. It is very effective to compare normal eyes to their own abnormal images side by side.

Dr. Choudhry: I also try to give patients some context about why they have this condition, because "Why do I have this?" is often one of their first questions. We talk about the influence of family history, genetic factors, such as light-colored skin or eyes, and choices, like smoking. The ways people acquire AMD are so multifaceted that the origin can be a difficult concept for people to grasp.

Prof. Holz: We talked about the genesis of this term "dry AMD" and how it is still being used in the community. We all have to get better about what we say, because if we tell patients they have dry AMD the relatives look it up, they see a major cause of severe visual loss linked to GA. It is a miseducation for many people who will never lose vision from earlier stages. We have to be extremely careful about how we use the term.

Prof. Guymer: I tell patients that it is sort of like finding high blood pressure. You feel fine, but you are at risk of a stroke or a heart attack, and that could happen in the future. I explain that early or intermediate AMD is not late AMD, but they are at risk of progressing to late AMD and experiencing vision loss as a result. I am also careful when I am injecting patients with anti-VEGF therapy to not say something like, "Great, you have a dry retina," which they could confuse with dry AMD.

▶ Do you get into the detailed types and the levels of AMD based on the classification system?

Dr. Choudhry: I usually do not, particularly at the initial consultation. Some people are more curious than others, but this is a lot to take in, and it is often over their heads. When patients are diagnosed, I think it is enough to describe the nature of exudative and nonexudative AMD to patients and alert them to the warning signs they need to watch for—namely, visual changes that could indicate progression. Those details, along with the context of their own lifestyle risk factors, make them feel confident they know what is going on and feel empowered to make decisions about their lifestyles and when to seek help.

Prof. Holz: General knowledge of the eye tends to be low. We are all working in our countries to improve awareness of the disease through different measures. As Dr. Singh pointed out, even the term "retina" is often unknown, as is "macula." I have heard many patients say, "I have macula." They think it

is a disease. We are working hard with patient organizations to improve the level of knowledge and awareness, as has been done in other fields of medicine. The most important thing we can do is to teach patients to see the doctor about any vision changes because early detection depends on how people interpret their vision deficits.

Prof. Guymer: Once my patients have been diagnosed and understand AMD, I begin showing them their images from visit to visit, to both teach and reassure them. When they come in for their yearly visit, they are quite keen to look at the drusen on their OCT. I explain that drusen come and go and that does not matter. I am looking for nascent GA, and if they do not have it, then they are stable. I also show them autofluorescence. I explain that I am looking for a mottled pattern that would indicate "RPD," and if I do not see it, that is a good sign. It means that they do not seem to have certain high-risk factors.

▶ Do any of you mention the possibility of a laser treatment for AMD?

Dr. Chow: When I discuss laser treatment with patients referred to me for the 2RT, I use a garbage truck analogy. The RPE cells are like garbage trucks, and these little spots I am showing them on the picture are building up because the garbage trucks are breaking down. With the 2RT laser, we try to reinvigorate those garbage trucks to get rid of the garbage again. My patients all smile at the garbage truck story, and it makes laser treatment for this complex disease easy to understand.

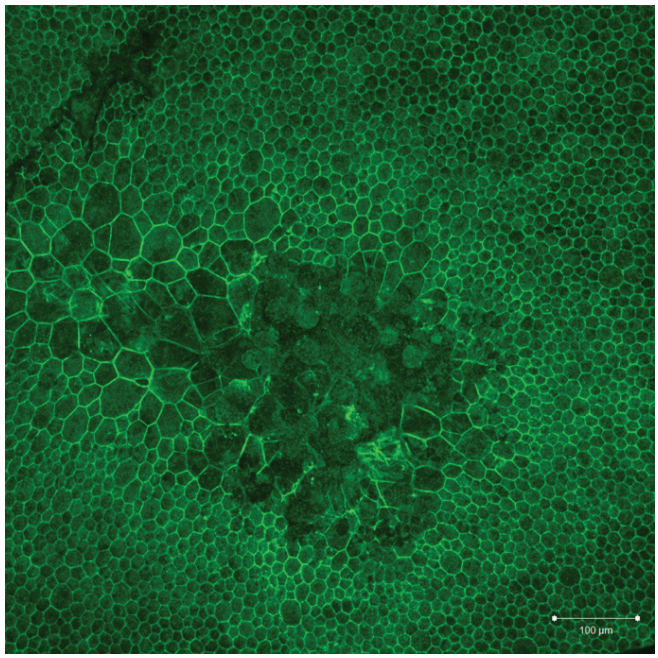
Dr. Choudhry: We are still early in the adoption phase. We have read that the treatment is cutting edge, and we are working towards educating our primary eye care colleagues about which types of patients should be considered for 2RT laser treatment. We generally are not discussing it with patients until we put that process in place.

POTENTIAL FOR FUTURE STUDIES OF 2RT

▶ Are you currently treating patients with 2RT or enrolling patients in studies within your practice?

Dr. Chow: There are many variables to be studied and a great deal of technique-related study opportunities, but I think before we get there, we want to ensure we are doing no harm.

Prof. Guymer: That is good point. For example, we do not really know whether we have to treat patients with the laser more than once. We think it works by causing RPE to divide (Figure 5), as shown in the results of preclinical studies. If that works, then maybe we do not need to do it very often. We have made a 70-year-old RPE into a 35-year-old RPE, and that might be enough. If it is not as effective as we want, do we have to repeat it? Should we change the dose? In the LEAD study, we chose to retreat patients, but we did not change the dose.



Courtesy of Robyn Guymer AM, MBBS, PhD.

Figure 5. RPE cells treated with the 2RT laser shown to be migrating and dividing in the eye.

Dr. Chow: In the LEAD study, you delivered 400 µm subthreshold laser spots at 12 locations on the retina—six each in the arcs above and below the superior and inferior vascular arcades. Retreatment was based on 6-month evaluations up to 30 months. How did you arrive at the number and location of those spots? Did you play around with doubling or tripling them?

Prof. Guymer: We chose to do 12 spots because that is what was done in thermal laser studies. I was also involved in the pilot study, and when we treated 50 people at 1,000 µm from the fovea, it became quite clear that we did not need to be that close. We moved out a bit to be safer.

By doing 12 spots, repeated if necessary, based on 6-month follow-up visits, we could scatter the spots for retreatment, rather than going over the same area again. John Marshall, PhD, FRCPath(Hon), from the United Kingdom, who came up with the concept that causing the RPE to reinvigorate would have a beneficial effect, would like us to do more spots. We are trying 100 spots now in a small pilot study. Again, we are looking at dark adaption as the safety signal, hoping to do some good by improving dark adaptation, but certainly making sure we are not making it worse.

Remember that benefits of 2RT treatment come from removing a few RPE cells in a disease where the RPE is not functioning properly. When RPD are present, the RPE cells are being overly stressed, and the RPE is failing to deal with the debris accumulating at both sides.

WOULD YOU RECOMMEND 2RT FOR YOURSELF OR A LOVED ONE?

▶ **If you had intermediate AMD, or a loved one had it, would you want 2RT treatment to be done?**

Prof. Guymer: I would involve them in the next study.

Prof. Holz: Agreed. I would enroll them in the next study and explore the many ideas we have discussed for studying further aspects of this treatment.

Dr. Chow: I am going to sound overly aggressive, but I would actually treat them. The major caveat would be if my family member had RPD all over the place, in which case I would say, "Not right now." But if my mother did not have RPD, and she were starting to notice a loss of vision, I would treat with 2RT. We see patients all the time who are losing vision, and they know it. They are begging us to do something. Now instead of telling those patients, "Sorry, I do not have anything," I would treat with 2RT in the absence of RPD.

Dr. Singh: The data are mounting. My choice would depend on the long-term results of the LEAD study, so we can see if patients progress to neovascular AMD or GA over time.

Dr. Choudhry: My thoughts are not that different from the rest of our group. I would want to see more data first. We all practice to do no harm, which is why we do studies to determine where there is harm and where there is safety for the patient. I think thus far, we have seen some markers for safety with the LEAD study, and the mounting data ultimately seem promising for offering 2RT treatment. ■

1. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2:e106-116.
2. World Health Organization (WHO). Global Initiative for the Elimination of Avoidable Blindness: action plan 2006-2011. WHO. 2007.
3. Ferris FL 3rd, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120(4):844-851.
4. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. *Ophthalmology*. 2018;125(4):537-548.
5. Guymer RH, Wu Z, Hodgson LAB, et al. Subthreshold nanosecond laser intervention in age-related macular degeneration: the LEAD randomized controlled clinical trial. *Ophthalmology*. 2018;pii:S0161-6420(18):32135-3.
6. Finger RP, Wu Z, Luu CD, et al. Reticular pseudodrusen: a risk factor for geographic atrophy in fellow eyes of individuals with unilateral choroidal neovascularization. *Ophthalmology*. 2014;121(6):1252-1256.
7. Sivaprasad S, Bird A, Nitiahpapand R, et al. Perspectives on reticular pseudodrusen in age-related macular degeneration. *Surv Ophthalmol*. 2016;61(5):521-537.
8. Curcio CA, Messinger JD, Sloan KR, McGwin G, Medeiros NE, Spaide RF. Subretinal drusenoid deposits in non-neovascular age-related macular degeneration: morphology, prevalence, topography, and biogenesis model. *Retina*. 2013;33(2):265-276.
9. Chew EY, Clemons TE, Bressler SB, et al. Randomized trial of a home monitoring system for early detection of choroidal neovascularization home monitoring of the Eye (HOME) study. *Ophthalmology*. 2014;121(2):535-544.
10. Jobling AI, Guymer RH, Vessey KA, et al. Nanosecond laser therapy reverses pathologic and molecular changes in age-related macular degeneration without retinal damage. *FASEB J*. 2015;29(2):696-710.
11. Guymer RH, Brassington KH, Dimitrov P, et al. Nanosecond-laser application in intermediate AMD: 12-month results of fundus appearance and macular function. *Clin Exp Ophthalmol*. 2014;42(5):466-479.
12. Chew EY, Clemons T, SanGiovanni JP, et al. The Age-Related Eye Disease Study 2 (AREDS2): Study Design and Baseline Characteristics (AREDS2 Report Number 1). *Ophthalmology*. 2012;119(11): 2282–2289.
13. Gass JD. Photocoagulation of macular lesions. *Trans Am Acad Ophthalmol Otolaryngol*. 1971;75:580e608.
14. Virgili G, Michelessi M, Parodi MB, et al. Laser treatment of drusen to prevent progression to advanced age-related macular degeneration. *Cochrane Database Syst Rev*. 2015;10:CD006537.

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